

N-Phenylpyrazole-based anti-flea and anti-tick collar
for cats and dogs

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5. The present invention relates to an external antiparasitic device, in particular a collar, for pets, in particular cats and dogs, this collar being active against the ectoparasites of these animals, in particular fleas and ticks.

10. The invention also relates to the use of active compounds for the manufacture of such collars or external devices, as well as to a treatment process relating thereto.

15. The invention is directed mainly towards fleas of the genus Ctenocephalides, in particular C. felis and C. canis, and ticks, in particular of the genus Rhipicephalus, especially sanguineus, as well as harvest ticks (*Trombicula automnalis*), which are acarids that mainly attack hunting dogs.

20. Collars intended to eliminate common ectoparasites from cats and dogs have been produced for a long time. These collars consist of a matrix, usually a plastic matrix, which incorporates between 5 and 40% active substance and is capable of releasing it over 25. time. These collars thus theoretically have the aim of ensuring long-lasting protection.

30. However, despite the activity claims, out in the field the collars do not have the efficacy required to ensure the actual elimination of these parasites. The cause of this may be the low activity of the active substance included in the matrix. Another cause may be

the accelerated degradation of these active substances under the effect of climatic factors, such as light, heat and rain. Lastly, control of the release of the active substance from the matrix is largely overevaluated. Release generally proves to be difficult and variable, and may depend greatly on the manufacturing conditions, which may vary from one batch to another, and on the conditions of use, in particular climatic variations and especially humidity and temperature, etc. In addition, only a relatively small amount of the active substance incorporated is actually released and it proves difficult to be able to control and optimize its release.

Another drawback of the collars encountered in practice arises from the mode of use of this device which may, obviously, be taken off, worn irregularly, or even be pulled off when the animal moves about, for example in undergrowth; the problem is particularly critical for hunting dogs whose collars are removed before a hunting outing even though they will be confronted with a flea- and tick-ridden environment.

Patent applications WO-A-87/03781 and EP-A-0,295,117 have proposed insecticides of the N-phenyl-pyrazole class.

These substances are described as being active against a very large number of parasites encountered in various fields, namely agriculture, public health and human and veterinary medicine. In the latter field, these substances may act in particular against the fleas and ticks of pets, such as cats and dogs. These substances may be applied in various ways, namely via the oral, parenteral, percutaneous or topical route. The latter type of administration itself covers many

possibilities, namely sprays, powders, baths, showers, jets, greases, shampoos, creams, waxes, preparations of skin solution type (pour-on) and external devices such as earrings and collars to provide local or systemic treatment. EP-A-0,295,117 and EP-A-0,500,209 propose a slow release composition which may be in the form of a collar or earrings for controlling harmful insects. Such a formulation may comprise from ~0.5~ to ~25~ active material, from 75 to 99.5% polyvinyl chloride and a catalytic amount of a plasticizer, dioctyl phthalate.

French patent application FR-A-2,713,889 describes a pesticide composition containing an insect growth regulator and an N-aryldiazole derivative chosen from the derivatives 4-(2-bromo-1,1,2,2-tetrafluoroethyl)-1-(3-chloro-5-trifluoromethylpyridine-2-yl)-2-methylimidazole, 5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylsulphinylpypyrazole and 5-amino-3-cyano-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-trifluoromethylthiopyrazole. As in the prior documents discussed above, the compositions are directed towards a large number of insects in different fields, and various types of formulations. Dog fleas and cat fleas are targeted. Among the formulations proposed, this document mentions resinous preparations which may be made into pesticide collars for animals.

However, none of these documents describes the use of pesticidal collars comprising a compound of the N-phenylpyrazole family to control fleas and ticks on pets such as cats and dogs, which make it possible to ensure a high level of efficacy for a long period against these parasites.

As for the pesticidal compounds of the prior art, a specialist might have expected to encounter

conventional problems of release from the collars and thus problems of activity.

After all, French patent application FR-A-2,713,889 proposes, does it not, the combination of such 5 compounds with an insect growth regulator?

The publications C. Genchi et al., Professione Veterinaria No. 1, supplement 1995, pages 19 to 10 22, J.M. Postal, Professione Veterinaria No. 1, supplement 1995, pages 17 and 18 and A. Searle et al., Australian Veterinary Practitioner, volume 25, No. 3, 1995, pages 157 and 158 propose instead to effectively control fleas and ticks using a sprayable solution (spray) containing this type of active compound.

The Applicant has now found, surprisingly, 15 that despite the fact that these N-phenylpyrazoles encounter the same difficulties of release as the products of the prior art, it is however possible to obtain collars which are entirely effective for the elimination 20 of cat and dog ectoparasites over a very long period, for example from 6 to 18 months, and that, in addition, the efficacy persists long after the collar is taken off, namely over a period which may be equal to or exceed 2 months, such that it is then possible to obtain 25 a collar which is entirely effective irrespective of the conditions of use. On account of the fact that the protection persists after the collar is taken off, it may be understood that irregular or voluntary use or that resulting from loss of the collar does not jeopardize the protection from which the animal should benefit.

In addition, the Applicant has observed that this long-lasting efficacy was obtained with concentrations of active substance in the matrix forming the

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5 collar which were much smaller than those of the standard products. It was also observed that this efficacy was obtained within a very short time of the collars being put on, in particular an efficacy of greater than 95% in 24 h against fleas and greater than 90% in 48 h against ticks.

It was observed, very surprisingly, that the compounds according to the invention, which are very lipophilic and of high vapour pressure (low volatility), had a very high affinity for the sebum which usually covers the animal's coat (skin and hair), such that, when released, this compound is taken up by the sebum, after which a translocation phenomenon occurs ensuring distribution of active substance over the animal's entire body. In addition, and this is a noteworthy point, these active substances become concentrated in the sebaceous glands which become a reservoir for them, ensuring very long-lasting efficacy and making it possible to compensate for the absence of the collar, by releasing the active substance by passive diffusion.

By virtue of this phenomenon, the variations in release of the active substance by the collar on account of, for example, a variation in climatic conditions, are compensated for by the possibilities of release by the sebaceous glands.

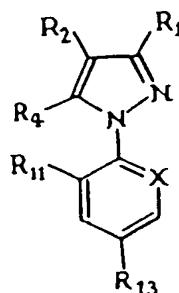
It was also observed that after a bath, which could possibly lead to the removal of the sebum distributed over the animal's body, the animal very rapidly became reprotected, in the presence or absence of the collar, owing to the fact that secretion of new sebum is accompanied by a release, by the sebaceous glands, of the active substance that they contain.

The subject of the present invention is thus

a collar or other external device for a pet, in particular a cat or dog, made of a matrix in which is incorporated from 0.1 to 40% by weight, relative to the collar, of a substance which is active against ectoparasites such as fleas and ticks (anti-flea and anti-tick collar or other external device), this active substance being formed of at least one compound corresponding to formula (I) below:

10

15



(I)

in which:

20 R_1 is CN or methyl or a halogen atom;

R_2 is $S(O)_nR_3$ or 4,5-dicyanoimidazol-2-yl or haloalkyl;

R_3 is alkyl or haloalkyl;

25 R_4 represents a hydrogen or halogen atom; or a radical NR_5R_6 , $S(O)_mR_7$, $C(O)R_7$, $C(O)O-R_7$, alkyl, haloalkyl or OR_8 or a radical $-N=C(R_9)(R_{10})$;

30 R_5 and R_6 independently represent a hydrogen atom or an alkyl, haloalkyl, $C(O)alkyl$, alkoxy carbonyl or $S(O)_rCF_3$ radical; or R_5 and R_6 may together form a divalent alkylene radical which may be interrupted by one or two divalent hetero atoms, such as oxygen or sulphur;

R_7 represents an alkyl or haloalkyl radical;

R₈ represents an alkyl or haloalkyl radical or a hydrogen atom;

R₉ represents an alkyl radical or a hydrogen atom;

5 R₁₀ represents a phenyl or heteroaryl group optionally substituted with one or more halogen atoms or groups such as OH, -O-alkyl, -S-alkyl, cyano or alkyl;

10 R₁₁ and R₁₂ represent, independently of each other, a hydrogen or halogen atom, or optionally CN or NO₂;

R₁₃ represents a halogen atom or a haloalkyl, haloalkoxy, S(O)_qCF₃ or SF₅ group;

m, n, q and r represent, independently of each other, an integer equal to 0, 1 or 2;

15 X represents a trivalent nitrogen atom or a radical C-R₁₂, the other three valency positions of the carbon atom forming part of the aromatic ring;

20 with the proviso that when R₁ is methyl, either R₃ is haloalkyl, R₄ is NH₂, R₁₁ is Cl, R₁₃ is CF₃ and X is N; or R₂ is 4,5-dicyanoimidazol-2-yl, R₄ is Cl, R₁₁ is Cl, R₁₃ is CF₃ and X is =C-Cl;

25 this collar or other external device being designed to ensure at least more than 6 months of efficacy against fleas and at least more than 3 months of efficacy against ticks, the efficacy preferably being maintained for several weeks even if the collar or other external device is taken off or lost or if there is a variation in the rate of release of the compound (I) by the matrix.

30 Preferably, in formula (I),
R₁ is CN or methyl;
R₂ is S(O)_nR₃;
R₃ is alkyl or haloalkyl;

R₄ represents a hydrogen or halogen atom; or a radical NR₅R₆, S(O)_mR₇, C(O)R₇, alkyl, haloalkyl or OR₈ or a radical -N=C(R₉)(R₁₀);

5 R₅ and R₆ independently represent a hydrogen atom or an alkyl, haloalkyl, C(O)alkyl or S(O)_rCF₃ radical; or R₅ and R₆ may together form a divalent alkylene radical which may be interrupted by one or two divalent hetero atoms, such as oxygen or sulphur;

10 R₇ represents an alkyl or haloalkyl radical; R₈ represents an alkyl or haloalkyl radical or a hydrogen atom;

R₉ represents an alkyl radical or a hydrogen atom;

15 R₁₀ represents a phenyl or heteroaryl group optionally substituted with one or more halogen atoms or groups such as OH, -O-alkyl, -S-alkyl, cyano or alkyl;

R₁₁ and R₁₂ represent, independently of each other, a hydrogen or halogen atom;

20 R₁₃ represents a halogen atom or a haloalkyl, haloalkoxy, S(O)_qCF₃ or SF₅ group;

m, n, q and r represent, independently of each other, an integer equal to 0, 1 or 2;

25 X represents a trivalent nitrogen atom or a radical C-R₁₂, the other three valency positions of the carbon atom forming part of the aromatic ring;

with the proviso that when R₁ is methyl, then R₃ is haloalkyl, R₄ is NH₂, R₁₁ is Cl, R₁₃ is CF₃ and X is N.

30 Compounds of formula (I) in which R₁ is CN will be selected most particularly. The compounds in which R₂ is S(O)_nR₃, preferably with n = 1, R₃ preferably being CF₃ or alkyl, for example methyl or ethyl, or alternatively n = 0, R₃ preferably being CF₃, as well as

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those in which $X = C-R_{12}$, R_{12} being a halogen atom, will also be selected. Compounds in which R_{11} is a halogen atom and those in which R_{13} is haloalkyl, preferably CF_3 , are also preferred. In the context of the present invention, compounds combining two or more of these characteristics will advantageously be selected.

A preferred class of compounds of formula (I) consists of compounds such that R_1 is CN , R_3 is haloalkyl, preferably CF_3 , or ethyl, R_4 is NH_2 , R_{11} and R_{12} are, independently of each other, a halogen atom, and/or R_{13} is haloalkyl.

In the present invention, the alkyl radicals may contain generally from 1 to 6 carbon atoms. The cycle formed by the divalent alkylene radical representing R_5 and R_6 , as well as with the nitrogen atom to which R_5 and R_6 are linked may be generally a cycle of 5, 6 or 7 links.

A compound of formula (I) which is most particularly preferred in the invention is

20 $1-[2,6-Cl_24-CF_3\text{phenyl}]3-CN\ 4-[SO-CF_3]5-NH_2\text{pyrazole}$,

which is referred to hereinbelow as compound A.

Mention may also be made of the two compounds which differ from the above A by the following characteristics:

25 1- $n = 0$, $R_3 = CF_3$

2- $n = 1$, $R_3 = \text{ethyl}$.

Compounds of formula (I) may be prepared according to one or other of the processes described in 30 patent applications WO-A-87/3781, 93/6089, 94/21606 or European patent application EP-A-0,295,117, or any other process falling within the competence of a specialist skilled in the art of chemical synthesis. For the

chemical preparation of the products of the invention, a person skilled in the art is considered as having at his disposal, inter alia, all of the contents of "Chemical Abstracts" and the documents which are cited therein.

5 However, low concentrations, of from 1 to 15% by weight and more particularly, especially for compound A, of from 1.25 to 10%, are preferred.

10 Under optimum conditions, compound (I) and especially compound A is present in the collar in a proportion of from 2 to 6% by weight, more particularly from 2.5 to 5% by weight.

15 It would obviously be possible to add to compound A any other insecticide which might be considered useful.

20 These insecticides may be present in the same matrix as the compound according to the invention. A composite collar made of at least two parts, each including a different active substance, may also be used.

25 Within the scope of the invention, matrices usually used to make collars may be used. Preferred examples which may be mentioned are matrices based on PVC (polyvinyl chloride), as described in US-A-3,318,769, 3,852,416 and 4,150,109 and 5,437,869, and other vinyl polymers.

30 The plasticizers may be chosen in particular from adipates, phthalates, phosphates and citrates.

35 One or more plasticizers will preferably be added to the PVC, these plasticizers being chosen in particular from the following compounds:

- diethyl phthalate
- dioctyl sebacate

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- dioctyl adipate
- diisodecyl phthalate
- acetyl tributyl citrate
- diethyl hexyl phthalate
- 5 - di-n-butyl phthalate
- benzyl butyl phthalate
- acetyl tributyl citrate
- tricresyl phosphate
- 2-ethylhexyl diphenyl phosphate.

10 Even more preferably, a PVC matrix will be used in the presence of a primary remanent plasticizer and a secondary plasticizer, in particular according to EP-A-0,539,295 and EP-A-0,537,998.

15 Among the secondary plasticizers, mention may be made of the following products:

- acetyl triethyl citrate
- triethyl citrate
- triacetin
- diethylene glycol monoethyl ether
- 20 - triphenyl phosphate.

A common stabilizer may also be added thereto.

25 For the purposes of the present invention, the term external device should be understood to refer to any device which can be attached externally to the animal in order to provide the same function as a collar.

30 By varying the concentration and/or composition of the matrix, collars or other external devices according to the invention, which ensure effective and long-lasting protection against fleas, may be made. Collars or other external devices may be made with an efficacy of greater than 6 months, in particular

of greater than or equal to 12 or 18 months, even when the collar or external device is taken off for a relatively prolonged period. When the collar or device is taken off, the duration of effective protection may range from 2 to 3 months.

By varying the concentration and/or composition of the matrix, it is possible to make collars or other external devices according to the invention which ensure effective and long-lasting protection against ticks. Collars or external devices may be made with an efficacy of greater than 3 months, in particular of greater than or equal to 12 or 15 months, even when the collar or external device is taken off for a relatively prolonged period. When the collar or external device is taken off, the duration of effective protection may range from 1 to 2 months.

It is noteworthy that this very long-lasting and total efficacy is obtained by the compound according to the invention alone, without addition of another insecticide.

The subject of the present invention is also a method for eliminating ectoparasites, in particular fleas and ticks, from pets such as cats and dogs, in which method at least one collar or other external device in accordance with the invention is attached to the animal and the animal is afforded long-lasting, effective protection against these parasites, even when the collar or other external device is taken off. The method is capable of ensuring prevention and treating fleas and ticks to a high degree of efficacy and over a period exceeding 6 months against fleas and 3 months against ticks, the efficacy preferably being maintained over several weeks even if the collar or external device

is taken off or if there is a variation in the release of the compound (I) by the collar or external device. The indications of duration have been given above. Preferably, it is recommended that, in accordance with 5 the method according to the invention, after it has been put on for the first time, the collar or external device should remain on the animal for at least 24 hours in order for sufficient active substance to pass to the animal and for the sebaceous glands to have been able to 10 store this active substance.

The object of this method is non-therapeutic and in particular relates to the cleaning of animal hairs and skin by elimination of the parasites which are present, as well as their residues and dejections. The 15 treated animals thus have hair which is more pleasant to look at and to feel.

The invention also relates to such a method for therapeutic purposes, intended to treat and prevent parasitoses having pathogenic consequences.

The subject of the present invention is also 20 the use of a compound corresponding to formula I for the production of a collar or other external device intended to be attached to a pet, in particular cats and dogs, this compound being capable of ensuring prevention and 25 treating fleas and ticks to a high degree of efficacy and over a period exceeding 6 months against fleas and 3 months against ticks, the efficacy preferably being maintained for several weeks if the collar or the external device is taken off or lost or if there is a 30 variation in the release of the compound (I) by the collar or the external device. The devices as above are concerned.

In particular, the method and device accor-

ding to the invention are designed to provide for an efficacy of greater than 95%, or even greater than 98 or 99% against fleas.

For ticks, the desired efficacy exceeds 80%
5 or 90%.

Similarly, the invention, against fleas, is directed towards the production of a long-lasting efficacy, longer than or equal to 12 months and even to 18 months.

10 For ticks, this duration is longer than 12 months, or even longer than 15 months.

Also preferably, the invention is directed towards the production of collars or other external devices which make it possible to obtain an efficacy maintained in the absence of the collar or external device over a period ranging from 2 to 3 months, or more, against fleas and from 1 to 2 months, or more, against ticks.

The present invention will now be described in greater detail with the aid of non-limiting examples from which other particular features and advantages of the invention will emerge.

EXAMPLE 1:

Collar containing 10% compound A

25 The following two types of collar were prepared
26 (mixing and then extrusion):

| | | | |
|----|----------------|------------------------|-------|
| 30 | Formulation 1: | PVC | 50.0% |
| | | Stabilizer | 0.5% |
| | | Epoxidized soybean oil | 5.0% |
| | | Diisooctyl adipate | 34.5% |
| | | Compound A | 10.0% |
| | Formulation 2: | PVC | 50.0% |
| | | Stabilizer | 0.5% |

| | |
|------------------------------|-------|
| Epoxidized soybean oil . . . | 5.0% |
| 2-Ethylhexyl diphenyl | |
| phosphate | 34.5% |
| Compound A | 10.0% |

5 (% by weight).

For the tests, 9 adult dogs which had not received any insecticide or acaricide for at least 40 days were chosen. The dogs were washed with an insecticide-free shampoo and combed in order to remove any existing 10 parasites.

The dogs were divided into groups of three.

Group A:

Untreated controls

Group B:

15 Collar containing 10% compound A - formulation 1.

Group C:

Collar containing 10% compound A - formulation 2.

The dogs are infested with about 100 ± 10 20 Ctenocephalides felis cat fleas (Unfed cat fleas) and 50 ± 2 Rhipicephalus sanguineus ticks (Brown dog tick).

The treatment follows the following general schema:

DAY

-2 Infestation with the fleas and ticks.

0 Collars are put on.

25 2 Fleas and ticks are counted with a comb.

7 Infestation with ticks.

8 Infestation with fleas.

9 Counting with a comb

35 Infestation with ticks.

30 36 Infestation with fleas.

37 Counting with a comb.

63 Infestation with ticks.

64 Infestation with fleas.

65 Counting with a comb.

The same process is continued with infestation with fleas and ticks every month for as long as a satisfactory efficacy is observed.

5 Hair samples were taken on:

D 205 and D 261 for all the dogs.

The collars were taken off on D 149 on dogs 363 and 289, on D 177 for dogs 87 and 300 and on D 205 for dogs 256 and 335.

10 The concentrations of active substance according to the invention on the hairs which were obtained at D 205 and D 261 are presented in Tables 1 and 2 respectively, in $\mu\text{g/g}$ of hair.

15 Table 1: Concentration of active substance according to the invention on D 205.

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| DOG | CONCENTRATION ($\mu\text{g.g}^{-1}$) | | | | |
|-----|--|----------------|---------------|-------------------|------------------|
| | UNDER THE COLLAR | RIGHT FLANK | LEFT FLANK | MIDDLE OF BACK | LUMBAR REGION |
| No. | | | | | |
| 20 | GROUP B | | | | |
| | 363 | 18.63 | 3.11 | 2.33 | 1.73 |
| | 87 | 19.03 | 2.28 | 3.08 | 5.81 |
| | 256 | 14.66 | 3.04 | 3.01 | 2.48 |
| | | | | | 10.99 |
| | GROUP C | | | | |
| 25 | 289 | 27.47 | 11.75 | 15.19 | 8.99 |
| | 300 | 482.4 | 34.6 | 15.69 | 17.97 |
| | 335 | 257.4 | 23.86 | 28.86 | 22.8 |
| | | | | | 41.2 |

T17ix
30 Table 2: Concentration of active substance according to the invention, on hairs on D 261.

| DOG No. | UNDER THE COLLAR | CONCENTRATION ($\mu\text{g.g}^{-1}$) | | | |
|----------------|---------------------|--|---------------|-------------------|------------------|
| | | RIGHT FLANK | LEFT FLANK | MIDDLE OF BACK | LUMBAR REGION |
| GROUP B | | | | | |
| 5 | 363 | 0.94 | 0.65 | >0.29 | >0.39 |
| | 87 | 0.64 | 0.94 | >0.32 | >0.40 |
| | 256 | >0.97 | ND | 0.81 | 0.78 |
| GROUP C | | | | | |
| 10 | 289 | 3.16 | >0.75 | >0.59 | >0.60 |
| | 300 | 3.79 | >0.70 | 2.04 | 1.35 |
| | 335 | 1.84 | 1.67 | 2.99 | 4.61 |
| | | | | | 4.19 |

ND = Not determined.

15 A distribution of active substance over the hair is observed: the concentrations on the different areas are higher with the formulation of Group C and are relatively homogeneous from one area to another.

20 The concentrations of active substance are still detectable 16 weeks after the collar has been taken off and are still effective at that stage.

Tables 3, 4 and 5 make it possible to carry out a concentration/activity correlation.

Table 3: Concentration/activity relationship on D 149.

| 5 | DOG No. | CONCENTRATION ($\mu\text{g.g}^{-1}$) | | | ACTIVITY ⁽¹⁾ | |
|----|-------------------|--|-----------------|------|-------------------------|-------|
| | | UNDER THE COLLAR | BACK AND FLANKS | | FLEAS | TICKS |
| | | | AV. | MIN | MAX | |
| 10 | GROUP B 363 | 559.5 | 15.6 | 10.7 | 24.8 | 0 |
| | GROUP C 289 | 871.3 | 48.9 | 30.8 | 94.4 | 0 |

(1) Number of fleas and ticks present on the dog

Table 4: Concentration/activity relationship on D 205.

| 20 | DOG No. | CONCENTRATION ($\mu\text{g.g}^{-1}$) | | | ACTIVITY ⁽¹⁾ | |
|----|---------------------------------|--|----------------------|----------------------|-------------------------|--------------|
| | | UNDER THE COLLAR | BACK AND FLANKS | | FLEAS | TICKS |
| | | | AV. | MIN | MAX | |
| 25 | GROUP B 363 87 256 | 18.6 19.0 15.0 | 3.54 3.93 4.88 | 1.73 2.28 2.48 | 6.99 5.81 11.0 | 0 0 0 |
| | GROUP C 289 300 335 | 27.5 482.4 257.4 | 16.7 26.3 29.2 | 8.99 15.7 22.8 | 30.9 36.7 41.2 | 12 0 0 |

(1): Number of fleas and ticks present on the dog

Table 5: Concentration/activity relationship on D 261.

| 5 | DOG No. | CONCENTRATION ($\mu\text{g.g}^{-1}$) | | | ACTIVITY ⁽¹⁾ | |
|----|------------|--|-----------------|-------|-------------------------|----------|
| | | UNDER THE COLLAR | BACK AND FLANKS | | FLEAS | TICKS |
| | | | AV. | MIN | MAX | |
| | GROUP B | | | | | |
| 10 | 363 | 0.94 | >0.70 | >0.29 | 1.47 | 0 ... 21 |
| | 87 | 0.64 | <0.55 | <LOQ | 0.94 | 0 12 |
| | 256 | >0.97 | <0.76 | <LOQ | 0.81 | 1 24 |
| | GROUP C | | | | | |
| 15 | 289 | 3.16 | >0.99 | >0.59 | 2.03 | 0 28 |
| | 300 | 3.79 | >2.40 | >0.70 | 5.52 | 0 19 |
| | 335 | 1.84 | 3.37 | 1.67 | 4.61 | 0 3 |

(1): Number of fleas and ticks present on the dog

AV. = average

MIN = minimum

MAX = maximum

LOQ = limit of quantification = 0.25 $\mu\text{g/g}$

On D 261, the activity towards fleas is 100% on all the dogs, except for one dog (presence of a flea).

The minimum concentrations (on the hair) which are effective towards fleas and ticks are determined to be about:

- 20 micrograms per gram of hair for ticks

- 1 microgram per gram of hair for fleas.

An activity of at least 5 months for ticks and of at least 9 months for fleas is observed with these formulations.

EXAMPLE 2:

Dogs were divided up into 6 groups of 8 dogs:

35 - A: Control group: collar containing no active

substance.

- B: Reference product: commercial collar against fleas and ticks, containing 8% Chlorpyrifos (O,O-diethyl-O-(3,5,6-trichloro-2-pyridyl)phosphorothioate), referred to as ref. in the tables.

5 - C: Collar containing 2.5% compound A.

- D: Collar containing 5% compound A

- E: Collar containing 10% compound A

10 The collars were made with the same ingredients as in formulation 2 of Example 1, with, in addition, a pigment (titanium dioxide).

The tests follow the following schedule:

-2 Infestation with fleas and ticks

0 Collars are put on

15 2 Counting with a comb

7 Reinfestation with ticks

8 Reinfestation with fleas

9 Counting with a comb

35 Reinfestation with ticks

20 36 Reinfestation with fleas

37 Counting with a comb

The process is continued along these lines from month to month.

25 Infestations and reinfestations are carried out at a rate of:

100 \pm 10 fleas

50 \pm 3 ticks

Tables 6 and 7 give the average effectiveness results.

30 Table 6: Percentage effectiveness on fleas, calculated as a geometric mean

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| DAY | Ref. 8% | GROUPS TREATED | | |
|-----|------------|----------------|--------|--------|
| | | 2.5% | 5% | 10% |
| 5 | -5 | 0.0% | 9.3% | 0.0% |
| | 2 | 63.9% | 98.7% | 100.0% |
| | 9 | 96.3% | 100.0% | 100.0% |
| | 37 | 96.1% | 99.9% | 100.0% |
| | 65 | 99.1% | 100.0% | 100.0% |
| | 93 | 99.6% | 100.0% | 100.0% |
| 10 | 121 | 99.4% | 100.0% | 100.0% |
| | 149 | 98.3% | 100.0% | 100.0% |
| | 177 | 97.9% | 100.0% | 100.0% |
| | 205 | 98.5% | 100.0% | 100.0% |
| | 233 | 96.6% | 100.0% | 100.0% |
| 15 | 268 | 89.6% | 100.0% | 100.0% |
| | 289 | 68.4% | 100.0% | 100.0% |
| | 317 | 76.0% | 100.0% | 100.0% |
| | 345 | 79.5% | 100.0% | 100.0% |
| | 373 | - | 100.0% | 100.0% |
| 20 | 401 | - | 99.4% | 100.0% |
| | 429 | - | 99.2% | 99.8% |
| | 457 | - | 96.9% | 98.8% |
| | 485 | - | 96.7% | 98.2% |
| | 513 | - | 90.3% | 99.0% |
| 25 | 541 | - | - | 98.8% |
| | | | | 100.0% |

T 23: X

Table 7: Percentage effectiveness on ticks, calculated as a geometric mean

| 5 | DAY | GROUPS TREATED | | | |
|----|-----|----------------|-------|--------|--------|
| | | Ref. 8% | 2.5% | 5% | 10% |
| | -5 | 4.7% | 19.1% | 19.1% | 32.0% |
| | 2 | 34.5% | 67.0% | 100.0% | 98.5% |
| | 9 | 86.9% | 96.2% | 100.0% | 100.0% |
| | 37 | 0.0% | 27.2% | 95.4% | 95.4% |
| 10 | 65 | 31.7% | 85.0% | 100.0% | 95.8% |
| | 93 | 31.8% | 86.7% | 100.0% | 95.7% |
| | 121 | 65.2% | 91.3% | 88.8% | 92.1% |
| | 149 | 59.0% | 93.4% | 92.0% | 94.5% |
| | 177 | 67.2% | 84.9% | 95.3% | 95.2% |
| 15 | 205 | 62.0% | 86.2% | 100.0% | 98.4% |
| | 233 | 62.6% | 89.8% | 98.3% | 97.9% |
| | 268 | 57.5% | 77.4% | 98.2% | 99.5% |
| | 289 | 44.6% | 92.4% | 97.2% | 95.1% |
| | 317 | - | 74.5% | 85.6% | 92.4% |
| 20 | 345 | - | 88.1% | 98.8% | 98.0% |
| | 373 | - | 72.4% | 93.9% | 95.7% |
| | 401 | - | 63.4% | 98.5% | 93.6% |
| | 429 | - | 75.3% | 83.2% | 93.3% |
| | 457 | - | 62.4% | 84.1% | 86.7% |
| 25 | 485 | - | - | - | - |
| | 513 | - | - | - | - |
| | 541 | - | - | - | - |